Remarks

Applicants thank the Examiner for a clear and concise Office Action. To expedite prosecution, Applicants' representative will contact the Examiner to arrange for a telephonic interview.

Claims 1-16 were under examination. To speed allowance of claims drawn to a commercially important embodiment, claims 5 and 8 are amended, claims 1-4, 7, 11 and 14-16 are canceled, and new claims 17-25 are added. The claim amendments and cancellations do not indicate agreement with the arguments presented by the Office and are made without prejudice to prosecution of the subject matter of the claims prior to this amendment in this or a related application.

The present invention arises in part from the counterintuitive realization that administration of a basal replacement dose of glucagon to a patient taking insulin achieves the beneficial effect of preventing hypoglycemia by virtue of the buffering or blunting effects of glucagon without diminishing the beneficial effects of glucose regulation provided by insulin (see paragraph [0018] et seq.). The basal replacement dose is administered when the patient in a euglycemic state rather than to a patient in or entering a hypoglycemic state. The basal replacement dose of glucagon administered is significantly lower than the conventional glucagon dose (1 mg) administered for treatment of hypoglycemia.

Rejection Under 35 U.S.C. 112, First Paragraph

Claims 1-6 and 8-16 were rejected as not enabled. The Office argues the specification is not enabling for preventing hypoglycemia, because "prevent" is an absolute definition and it is accepted that most diseases cannot be totally prevented (Office Action, page 6, lines 7-13). Applicants disagree that "prevent" is an absolute definition, but to expedite prosecution, claim 5 has been amended to recite that the method is practiced to reduce the risk of insulin-induced hypoglycemia. Support for the recitation of reducing the risk of insulin-induced hypoglycemia by administering a basal replacement dose of glucagon is found in the specification at, e.g., paragraphs [0027] and [0028], and [0033].

Rejections Under 35 USC 102(e) and/or 35 USC 103(a)

All of the claims were rejected as anticipated in view of U.S. Pat. No. 6,572,442 (Houben *et al.*, "the '442 patent") or obvious in view of the '442 patent in combination with Trading et al. and Unger et al. Applicants respectfully traverse the rejections.

The '442 patent describes a system for using an electrocardiogram (ECG) sensor or an electroencephalogram (EEG) sensor to determine that a patient "has entered" or is "about to enter" a hypoglycemic state (see, e.g., col. 5-6, esp. lines 28-32). ECG or EEG signals are analyzed by a microprocessor and based on the analysis an agent such as insulin or glucagon may be administered to modify the patient's blood glucose level.

The system described in the '442 patent differs in several respects from the present invention. First, according to the present invention *a basal replacement dose* of glucagon is administered. This is not suggested by the '442 patent. Second, according to the present invention glucagon is administered to patients when they are euglycemic, as part of an ongoing treatment regimen to prevent (or reduce the incidence of) hypoglycemia. In contrast, the system of the '442 patent relates to rescue of a patient for whom a hypoglycemic event has already occurred or is imminent, e.g., to "identify the *onset* of hypoglycemic events so that a beneficial agent may be delivered" to a patient "before the patient slips into a state where he is himself unaware of the onset of hypoglycemia and in danger of slipping further into a hypoglycemic coma" (col. 11, lines 17-22, emphasis added). These and other differences between the claimed invention and the '442 patent are discussed in greater detail below, with reference to specific elements of the instant claims.

Claim 5, as amended, is directed to a method of reducing the risk of insulin-induced hypoglycemia by administering a *basal replacement dose* of glucagon to a patient. The goal is to provide a level of plasma glucagon approximating the normal basal level (about 50 to 150 picograms/ml plasma) and prevent an unopposed action of insulin (see, e.g., paragraph [0066]). As taught in the specification, a basal replacement dose can be delivered by intravenous infusion of glucagon at 0.10 to 5.00 ng glucagon/kg patient weight/min (see paragraphs [0027] and

[0028]). Alternatively, a basal replacement dose of glucagon can be given by other routes (e.g., subcutaneously or intramuscularly).

The basal replacement dose is quite low (e.g., 0.4 - 21 micrograms per hour for a 70 kg patient receiving an infusion) and not taught or suggested by the '442 patent. The '442 patent does not specify *any* particular dose of glucagon, and, accordingly, would be understand by one of skill in the art to refer to administration of the *conventional* (e.g., 1 mg) dose of glucagon normally administered to patients to treat hypoglycemia. Administration of a conventional dose results in plasma glucagon that peaks at about 8 nanograms/ml (see, paragraph [0053]) while glucagon administration according to the present invention results in plasma glucagon concentrations in the picogram range. The '442 patent did not describe and would not have led one of ordinary skill to the claimed method. Accordingly this rejection should be withdrawn.

Claim 9 depends from claim 5 and recites that the glucagon is administered to a euglycemic patient (a patient with a blood glucose level of from 70 - 110 mg/dL). Claim 9 finds support in the specification at, e.g., paragraph [0009] (treatment regimen maintains glucagon in range that is neither hyperglycemic nor hypoglycemic) and paragraphs [0064], [0065], [0086] and [0088] (methods of invention allow patient to maintain normal glycemic control such as fasting levels of 70-110 mg/dL and postprandial levels of 120-160 mg/dL; plasma levels of 70 - 110 mg/dL represent a normal fasting glucose level). Nothing in the '442 patent described or suggested administering glucagon to a patient with a normal glycemic level (see the '442 patent at col. 3, line 66, defining a normal glycemic level as from 64 to 90 mg/dL). Rather, the '442 patent describes administering glucagon just prior to a hypoglycemic event (col. 14, line 17), when a hypoglycemic event is imminent or has already occurred (col. 13, lines 51-53), at the onset of an event (col. 17, line 37), and the like. The '442 patent would not have led one of ordinary skill to administer glucagon to a person without hypoglycemic symptoms and with a normal blood glucose level. Accordingly this rejection should be withdrawn.

Claim 21 is directed to a method of reducing the risk of insulin-induced hypoglycemia in a diabetes patient by administering glucagon daily at bedtime. Support for the new claim is

found, for example, in paragraph [0066]. According to the present invention, glucagon is administered, not to rescue a patient experiencing actual or developing hypoglycemia, but as part of a regular diabetes treatment regimen to prevent or reduce the risk of insulin-induced hypoglycemia. Nothing in the '442 patent suggested this method. Accordingly this rejection should be withdrawn.

The remaining claims depend directly or indirectly from these base claims and, similarly, are neither described not suggested by the '442 patent.

Related Application

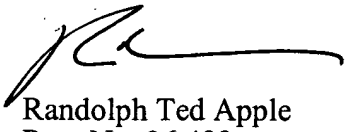
The Examiner is reminded that this application is an ancestor of copending application No. 11/169,825.

Conclusion

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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